IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I, VIVIEN IRENE COULSON, declare:

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland, residing at 96 Langley Road, Watford, Hertfordshire, WD17 4PJ;

2. That I am well acquainted with the French and English languages;

3. That the attached is a true translation into the English language of the certified copy of European Patent Application No. 03291931.8 filed 31 July 2003;

4. That I believe that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the patent application in the United States of America or any patent issuing thereon.

Declared this 6th day of October 2005

V.I. Coulson.

V.I. COULSON

European
Patent Office

Certificate

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Patent application No.

03291931.8

For the President of the
European Patent Office

[signature]

R C van Dijk

European
Patent Office

Application no.: 03291931.8 Date of filing: 31.07.03

Applicant(s):

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New process for the synthesis of perindopril and its pharmaceutically acceptable salts

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State/Date/File no.:

International Patent Classification:

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NEW PROCESS FOR THE SYNTHESIS OF PERINDOPRIL AND ITS PHARMACEUTICALLY ACCEPTABLE SALTS

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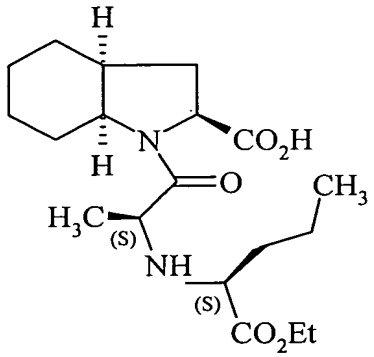
The present invention relates to a process for the industrial synthesis of perindopril of formula (I) :



(I)

and its pharmaceutically acceptable salts.

Perindopril and its pharmaceutically acceptable salts, and more especially its tert-butylamine salt, have valuable pharmacological properties.

Their principal property is that of inhibiting angiotensin I converting enzyme (or kininase II), which allows, on the one hand, prevention of the conversion of the decapeptide angiotensin I to the octapeptide angiotensin II (a vasoconstrictor) and, on the other hand, prevention of the degradation of bradykinin (a vasodilator) to an inactive peptide.

Those two actions contribute to the beneficial effects of perindopril in cardiovascular diseases, more especially in arterial hypertension and heart failure.

Perindopril, its preparation and its use in therapeutics have been described in European patent specification EP 0 049 658.

In view of the pharmaceutical value of this compound, it has been important to be able to obtain it by an effective industrial synthesis process, readily transposable to an industrial scale, that leads to perindopril in a good yield and with excellent purity starting from reasonably priced starting materials.

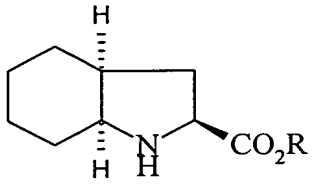
Patent specification EP 0 308 341 describes the industrial synthesis of perindopril by the coupling of (2*S*,3a*S*,7a*S*)-octahydroindole-2-carboxylic acid benzyl ester with N-[(S)-1-

carboxybutyl]-(S)-alanine ethyl ester, followed by deprotection of the carboxylic group of the heterocycle by catalytic hydrogenation.

The (2S,3aS,7aS)-octahydroindole-2-carboxylic acid ester is not a commercial product, and its preparation requires several synthesis steps (including a resolution step) starting from indole-2-carboxylic acid.

The Applicant has now developed a new process for the synthesis of perindopril that uses readily obtainable starting materials.

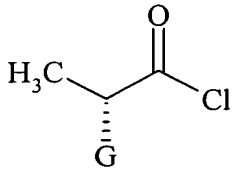
More specifically, the present invention relates to a process for the industrial synthesis of perindopril and its pharmaceutically acceptable salts which is characterised in that a compound of formula (II) :



(II) ,

wherein R represents a hydrogen atom or a benzyl or linear or branched (C_1-C_6)alkyl group,

is reacted with a compound of formula (III) having the (R) configuration :

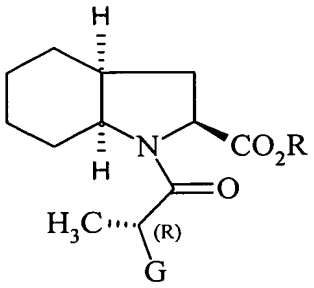


(III)

wherein G represents a chlorine or bromine atom or a hydroxy, p-toluenesulphonyloxy, methanesulphonyloxy or trifluoromethanesulphonyloxy group,

in the presence of a base,

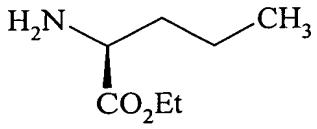
to yield a compound of formula (IV) :



(IV)

wherein R and G are as defined hereinbefore,

which is reacted with the compound of formula (V) :



(V)

to yield, after deprotection where necessary, the compound of formula (I).

Among the bases that can be used for the reaction between the compounds of formula (II) and (III) there may be mentioned, without implying any limitation, organic amines, such as triethylamine, pyridine and diisopropylethylamine, and mineral bases, such as NaOH, KOH, Na_2CO_3, K_2CO_3, $NaHCO_3$ and $KHCO_3$.

When G represents a chlorine or bromine atom, or a p-toluenesulphonyloxy, methanesulphonyloxy or trifluoromethanesulphonyloxy group, the reaction between the compounds of formulae (IV) and (V) is preferably carried out in the presence of a base, preferably an organic amine, such as triethylamine, pyridine or diisopropylethylamine, or a mineral base, such as Na_2CO_3, K_2CO_3, $NaHCO_3$ or $KHCO_3$.

When G represents a hydroxy group, the reaction between the compounds of formulae (IV) and (V) is preferably carried out in the presence of an activation reagent, such as N-methyl-N-phenyl-aminotriphenylphosphonium iodide, or hexamethylphosphorus triamide together with ammonium perchlorate, or, when R is other than a hydrogen atom, by Mitsunobu reaction.

The compounds of formula (IV) wherein G represents a chlorine atom or a p-toluenesulphonyloxy or methanesulphonyloxy group are new products which are useful as synthesis intermediates in the chemical or pharmaceutical industry, especially in the synthesis of perindopril, and as such form an integral part of the present invention.

EXAMPLE 1 : (2S,3aS,7aS)-1-{(2S)-2-[(1S)-1-(Ethoxycarbonyl)butylamino]-propionyl}octahydro-1*H*-indole-2-carboxylic acid tert-butylamine salt

Step A : *Benzyl (2S,3aS,7aS)-1-[(2R)-2-bromopropionyl]octahydro-1H-indole-2-carboxylate*

Introduce 200 g of benzyl (2S,3aS,7aS)-octahydro-1H-indole-2-carboxylate and 1.5 litres of dichloromethane into a reactor, then bring the temperature of the reaction mixture to 0°C and add 201 ml of diisopropylethylamine followed by 132 g of (2R)-2-bromo-propionyl chloride. Subsequently, bring the mixture to ambient temperature. After stirring for 1 hour at that temperature, wash the mixture with water and then with a dilute acetic acid solution. The benzyl (2S,3aS,7aS)-1-[(2R)-2-bromopropionyl]octahydro-1H-indole-2-carboxylate solution so obtained is used as it is in the following Step.

Step B : *Benzyl (2S,3aS,7aS)-1-{(2S)-2-[(1S)-1-(ethoxycarbonyl)butylamino]-propionyl}octahydro-1H-indole-2-carboxylate*

Introduce 123 g of ethyl (2S)-2-aminopentanoate, 160 ml of triethylamine and 160 ml of acetonitrile into a reactor, and then bring the mixture to 60°C, slowly add the solution obtained in Step A and reflux for 4 hours. After returning to ambient temperature, wash the mixture with water and with a dilute acetic acid solution, and then evaporate off the solvents to yield benzyl (2S,3aS,7aS)-1-{(2S)-2-[(1S)-1-(ethoxycarbonyl)butylamino]-propionyl}octahydro-1H-indole-2-carboxylate.

Step C : *(2S,3aS,7aS)-1-{(2S)-2-[(1S)-1-(Ethoxycarbonyl)butylamino]propionyl}-octahydro-1*H*-indole-2-carboxylic acid*

Introduce 200 g of the compound obtained in the above Step, in solution in acetic acid, and then 5 g of 10 % Pd/C into a hydrogenation vessel. Hydrogenate under a pressure of 0.5 bars at from 15 to 30°C until the theoretical amount of hydrogen has been absorbed. Remove the catalyst by filtration, and then cool to from 0 to 5°C and recover by filtration the solid obtained. Wash the cake and dry it to constant weight.
(2S,3aS,7aS)-1-{(2S)-2-[(1S)-1-(ethoxycarbonyl)butylamino]propionyl}octahydro-1*H*-indole-2-carboxylic acid is thereby obtained in a yield of 85 % and with an enantiomeric purity of 99 %.

Step D : *(2S,3aS,7aS)-1-{(2S)-2-[(1S)-1-(Ethoxycarbonyl)butylamino]propionyl}-octahydro-1*H*-indole-2-carboxylic acid tert-butylamine salt*

The precipitate obtained in the above Step (200 g) is dissolved in 2.8 litres of ethyl acetate, and then 40 g of tert-butylamine and 0.4 litres of ethyl acetate are added.
The suspension obtained is subsequently refluxed until complete dissolution occurs, and the solution obtained is then filtered in the heated state and cooled, with stirring, to a temperature of from 15 to 20°C.
The precipitate obtained is then filtered off, made into a paste again with ethyl acetate, dried and then crushed to yield the expected product in a yield of 95 %.

EXAMPLE 2 : (2S,3aS,7aS)-1-{(2S)-2-[(1S)-1-(Ethoxycarbonyl)butylamino]-propionyl}octahydro-1*H*-indole-2-carboxylic acid tert-butylamine salt

Step A : *(2S,3aS,7aS)-1-[(2R)-2-Bromopropionyl]octahydro-1H-indole-2-carboxylic acid*

Introduce into a reactor 200 g of (2S,3aS,7aS)-octahydro-1H-indole-2-carboxylic acid, 75 ml of water and 150 ml of toluene, and then bring the mixture to from 0 to 5°C and add 250 ml of 5M sodium hydroxide solution, followed by a solution of 202 g of (2R)-2-

bromopropionyl chloride in toluene, while maintaining the temperature below 10°C and maintaining the pH of the mixture at 10 by adding 5M sodium hydroxide solution. After stirring for a further 1 hour at 10°C, add concentrated hydrochloric acid to adjust the pH of the mixture to 6.

Separate off the toluene phase, and then add concentrated hydrochloric acid to the aqueous phase to adjust the pH to 2.

The precipitate formed is then filtered off and dried to yield (2S,3aS,7aS)-1-[(2R)-2-bromopropionyl]octahydro-1H-indole-2-carboxylic acid.

Step B : *(2S,3aS,7aS)-1-{(2S)-2-[(1S)-1-(Ethoxycarbonyl)butylamino]-propionyl}octahydro-1*H*-indole-2-carboxylic acid*

Introduce into a reactor 105 g of ethyl (2S)-2-aminopentanoate, 135 ml of triethylamine and 135 ml of acetonitrile, and then bring the mixture to 60°C and slowly add a solution of 200 g of the compound obtained in Step A in 1.3 litres of dichloromethane, and subsequently reflux for 4 hours. After returning to ambient temperature, wash the mixture with water and with a dilute acetic acid solution, and then evaporate off the solvents to yield (2S,3aS,7aS)-1-{(2S)-2-[(1S)-1-(ethoxycarbonyl)butylamino]propionyl}octahydro-1H-indole-2-carboxylic acid.

Step C : identical to Step D of Example 1.

EXAMPLE 3 : (2S,3aS,7aS)-1-{(2S)-2-[(1S)-1-(Ethoxycarbonyl)butylamino]-propionyl}octahydro-1*H*-indole-2-carboxylic acid tert-butylamine salt

Step A : *Benzyl (2S,3aS,7aS)-1-[(2R)-2-{p-toluenesulphonyloxy}propionyl]-octahydro-1H-indole-2-carboxylate*

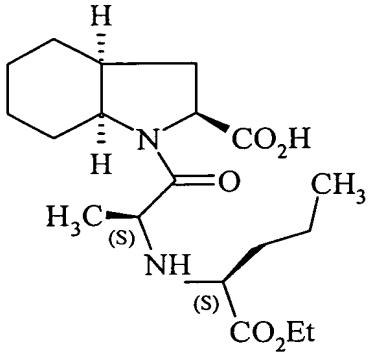
Introduce into a reactor 200 g of benzyl (2S,3aS,7aS)-octahydro-1H-indole-2-carboxylate and 1.5 litres of dichloromethane, and then bring the temperature of the reaction mixture to 0°C and add 201 ml of diisopropylethylamine, followed by 202 g of the chloride of (1R)-2-chloro-1-methyl-2-oxoethyl p-toluenesulphonate. Subsequently, bring the mixture to

ambient temperature. After stirring for 1 hour at that temperature, wash the mixture with water. The solution of benzyl (2S,3aS,7aS)-1-[(2R)-2-{p-toluenesulphonyloxy}propionyl]-octahydro-1H-indole-2-carboxylate so obtained is used as it is in the following Step.

Steps B to D : identical to Steps B to D of Example 1.

CLAIMS

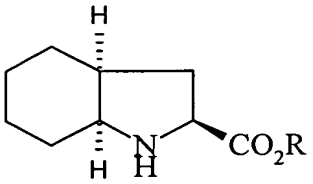
1. Process for the industrial synthesis of the compounds of formula (I) :



(I)

and its pharmaceutically acceptable salts,

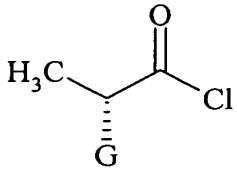
characterised in that a compound of formula (II) :



(II) ,

wherein R represents a hydrogen atom or a benzyl or linear or branched (C_1-C_6)alkyl group,

is reacted with a compound of formula (III) having the (R) configuration :

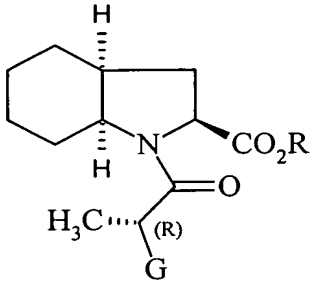


(III)

wherein G represents a chlorine or bromine atom or a hydroxy, p-toluenesulphonyloxy, methanesulphonyloxy or trifluoromethanesulphonyloxy group,

in the presence of a base,

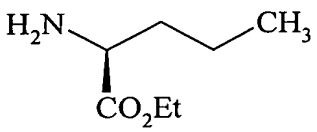
to yield a compound of formula (IV) :



(IV)

wherein R and G are as defined hereinbefore,

which is reacted with the compound of formula (V) :



(V)

to yield, after deprotection where necessary, the compound of formula (I).

2. Synthesis process according to claim 1, characterised in that the base used for the reaction between the compounds of formulae (II) and (III) is an organic amine selected from triethylamine, pyridine and diisopropylethylamine, or a mineral base selected from NaOH, KOH, Na_2CO_3, K_2CO_3, $NaHCO_3$ and $KHCO_3$.

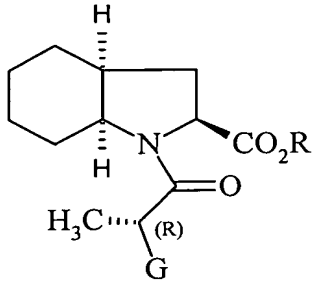
3. Synthesis process according to claim 1, characterised in that G represents a chlorine or bromine atom, or a p-toluenesulphonyloxy, methanesulphonyloxy or trifluoromethane-sulphonyloxy group.

4. Synthesis process according to claim 3, characterised in that the reaction between the compounds of formulae (IV) and (V) is carried out in the presence of an organic amine selected from triethylamine, pyridine and diisopropylethylamine, or of a mineral base selected from Na_2CO_3, K_2CO_3, $NaHCO_3$ and $KHCO_3$.

5. Synthesis process according to claim 1, characterised in that G represents a hydroxy group.

Synthesis process according to claim 5, characterised in that the reaction between the compounds of formulae (IV) and (V) is carried out in the presence of an activation reagent selected from N-methyl-N-phenyl-aminotriphenylphosphonium iodide and hexamethylphosphorus triamide together with ammonium perchlorate, or, when R is other than a hydrogen atom, by Mitsunobu reaction.

6. Compound of formula (IV) :



(IV)

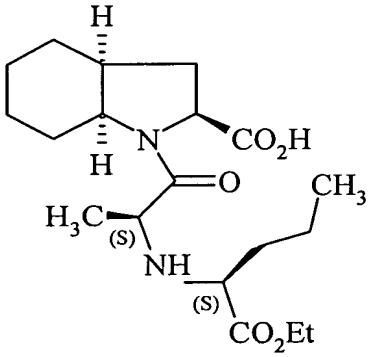
wherein R represents a hydrogen atom or a benzyl or linear or branched (C_1-C_6)alkyl group and G represents a chlorine atom or a p-toluenesulphonyloxy or methane-sulphonyloxy group.

7. Process according to any one of claims 1 to 6 for the synthesis of perindopril in the form of its tert-butylamine salt.

ABSTRACT

NEW PROCESS FOR THE SYNTHESIS OF PERINDOPRIL AND ITS PHARMACEUTICALLY ACCEPTABLE SALTS

Process for the industrial synthesis of perindopril of formula (I) :



(I)

and its pharmaceutically acceptable salts.